Beyond Antenatal Corticosteroids: What Did Mont Liggins Teach Us?

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The discipline of obstetrics and gynecology recently lost one of its greatest heroes. On August 24, 2010, Graham Liggins (above, right) passed away quietly in his hometown of Auckland, New Zealand, at the age of 84.

After finishing his clinical training at Auckland Hospital, Dr. Liggins (known to his friends as "Mont" after his childhood obsession with Monty the Mouse) chose to pursue a career in obstetrics and gynecology and soon became fascinated with the process of labor and birth. He was particularly interested in the mechanisms that induce parturition, and became convinced that it was the fetus and not the mother that was responsible for the timing of labor. After all, it was well known that fetuses lacking an intact hypothalamic-pituitary-adrenal axis (such as those with anencephaly or hypothalamic lesions) fail to go into labor at term. Looking around for an appropriate animal model on which to test his hypothesis, he naturally turned his attention to sheep. Even today, there are 13 sheep for every man, woman, and child in New Zealand. In a makeshift laboratory that he set up in an abandoned shed, Dr. Liggins began infusing sheep with corticosteroids to see what effect it had on the timing of labor. *And that was when a chance observation*

changed the course of obstetric history. One morning, Dr. Liggins discovered that a sheep he had infused with corticosteroids had delivered overnight. The lamb was so premature that it should not have survived, and yet there it was, alive and breathing.

In collaboration with his pediatric colleague, Dr. Ross Howie (previous page, left), Dr. Liggins went on to demonstrate that antenatal corticosteroids administered to pregnant women threatening to deliver prematurely cross the placenta and induce a wave of cellular differentiation that results in a 50% reduction in respiratory complications (the final organ system required for extrauterine life) and a comparable decrease in perinatal mortality. This discovery likely represents the single greatest collaboration between an obstetrician and pediatrician in medical history. There is no doubt that the intervention they described has saved the lives of hundreds of thousands of tiny premature infants and saved families and society from the personal and financial burden of a lifetime of caring for a handicapped child.

Although numerous studies have confirmed these observations, none have yet managed to improve on the timing and dosage regimens described by Liggins and Howie in their original manuscript, published in *Pediatrics* in 1972.[1] That said, a number of outstanding issues remain.[2] What is the optimal timing of antenatal steroid administration? How early in gestation can it be given? What is the best formulation? Should a repeat or "rescue" course be administered if the first course is given early in gestation? Is there any risk to the mother or fetus? What is the effect of antenatal steroids on long-term neurodevelopment in the offspring? Do they increase or decrease the risk of cerebral palsy? And—perhaps most importantly—exactly how do steroids work on a molecular level to promote cellular differentiation in the developing fetus? Sadly, Dr. Liggins is no longer around to help us answer these questions. We are going to have to solve them on our own.

So what exactly is Dr. Liggins's legacy? There is no doubt that his incidental finding of the beneficial effects of antenatal corticosteroids is one of the most important discoveries in obstetrics, and an entire generation of premature infants and their families owe him a debt of gratitude. But there are additional lessons that can be learned even by those of us who have not been touched personally by his discoveries:

- *Medical advances are universal*. Dr. Liggins made his discovery in a tiny abandoned shed on the north island of New Zealand. Despite publishing his findings in a highly credible scientific journal, it took more than 20 years for this intervention to find its way into routine clinical practice in the United States. When asked about this, Dr. Liggins once said it was likely because people thought nothing good could come out of the colonies. We need to learn that medical advances are universal. It matters not where in the world a medical breakthrough is made, who makes it, or in what language it is published. Every effort should be made to identify major medical advances early and to work to incorporate them into routine clinical practice in a more timely fashion.
- *Animal models can and should be used to test scientific hypotheses*. Humans are not mice or sheep, and not all scientific observations in animal models can be translated to humans. This is one example in which the appropriate and judicious use of an animal model resulted in a more rapid transition into human clinical trials and, ultimately, into routine clinical practice.
- *Be prepared for serendipity*. The discovery of the beneficial effects of antenatal steroids could easily have been missed had it not been for Dr. Liggins's astute power of observation and intellectual curiosity. In the words of Yogi Berra: "You can see a lot just by observing."
- *The power of humility*. The professional legacy that each of us leaves behind has more to do with the quality of the care/research that we provide and the ability to pass this on to the next generation than the accolades we receive while we are alive. By all reports, Dr. Liggins was a humble and generous man. Although he was awarded a fellowship of the Royal Society in 1980 and a knighthood in 1991, the extent of his scientific advances that have saved the lives of hundreds of thousands of premature infants would have made Dr. Liggins a popular recipient of the Nobel Prize. Alas, this honor eluded him. But his name and reputation will continue to live on for many years to come. ■

References

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